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Low-fat dietary pattern and global cognitive function: Exploratory analyses of the Women's Health Initiative (WHI) randomized Dietary Modification trial

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A B S T R A C T

Background: Meta-analyses of observational studies associate adherence to several dietary patterns with cognitive health. However, limited evidence from full scale, randomized controlled trials precludes causal inference regarding dietary effects on cognitive function.
Methods: The Women's Health Initiative (WHI) Dietary Modification (DM) randomized trial, in 48,835 postmenopausal women, included a subset of 1,606 WHI Memory Study (WHIMS) participants >= 65 years old, to assess low-fat dietary pattern influence on global cognitive function, evaluated with annual screening (Modified Mini−Mental State Examinations [3MSE]). Participants were randomized by a computerized, permuted block algorithm, stratified by age group and center, to a dietary intervention (40%) to reduce fat intake to 20% of energy and increase fruit, vegetable and grain intake or usual diet comparison groups (60%). The study outcome was possible cognition impairment (failed cognitive function screening) through the 8.5 year (median) dietary intervention. Those failing screening received a comprehensive, multi-phase cognitive function assessment to classify as: no cognitive impairment, mild cognitive impairment, or probable dementia. Exploratory analyses examined the composite endpoint of death after possible cognitive impairment through 18.7 years (median) follow-up. The WHI trials are registered at ClinicalTrials.gov:NCT00000611.
Findings: Among the 1,606 WHIMS participants, the dietary intervention statistically significantly reduced the incidence of possible cognitive impairment (n = 126; hazard ratio [HR] 0.59 95% confidence interval [CI] 0.38−0. 91, P = 0.01) with HR for dietary influence on subsequent mild cognitive impairment of 0.65 (95% CI 0.35−1.19) and HR of 0.63 (95% CI 0.19−2.10) for probable dementia (PD). Through 18.7 years, deaths from all-causes after possible cognitive impairment were non-significantly lower in the dietary intervention group (0.56% vs 0.77%, HR 0.83 95% CI 0.35 to 2.00, P = 0.16).
Interpretation: Adoption of a low-fat eating pattern, representing dietary moderation, significantly reduced risk of possible cognitive impairment in postmenopausal women.
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Research in context

Evidence before this study

Cognitive dysfunction and dementia represent major health risks in women as they age. Observational studies have associated several dietary patterns with cognitive health. However, few randomized trials have evaluated dietary influence on cognition. The 2010 NIH Report on Preventing Alzheimer's Disease and Cognitive Decline noted a critical need for randomized trials in this area and proposed criteria for such trials. To our review, the four trials meeting these criteria have limitations of short intervention durations and absence of long term follow-up. Against this background, we provide findings from a large (n = 1606) subgroup of postmenopausal women participating in the Women's Health Initiative (WH)I Memory Study (WHIMS) who were among the 48,835 women in the WHI Dietary Modification (DM) trial evaluating the potential influence of a low-fat dietary pattern on cognitive impairment.

Added value of this study

WHIMS participants, between 65 and 79 years old, were randomized to dietary intervention with a target of fat intake reduction and increase in fruits, vegetables and grains or usual diet comparison groups. Annual cognitive function screening through 8.5 years (median) intervention was based on Modified Mini-Mental Examinations [3MSE]. The study endpoint was possible cognitive impairment (failed 3MSE screening). Those with failed screening received a comprehensive, multi-phase neuropsychological evaluation and were followed for clinical outcome. In contrast to the comparison group, women in the dietary intervention group had a significantly decreased risk of possible cognitive impairment (hazard ratio [HR] 0.59 95% confidence interval [CI] 0.38−0.91, P = 0.01). Through 18.7 years, deaths from all-causes after possible cognitive impairment were non-significantly lower in the dietary intervention group (0.56% vs 0.77%, HR 0.83 95% CI 0.35 to 2.00, P = 0.16).

Implications of the available evidence

Our current findings provide prospective, randomized clinical trial evidence that adoption of a low-fat dietary pattern, representing dietary moderation, significantly reduced risk of possible cognitive impairment in postmenopausal women. Our study design, duration of the dietary intervention and length of follow-up, substantially strengthens evidence that a dietary pattern can influence cognitive function and identifies fat intake reduction as a component of the dietary pattern.

1. Introduction

Late-age development of cognitive impairment and dementia represent major health risks, especially in women where about two thirds of cases are seen [1]. The World Health Organization (WHO) and others have emphasized the importance of development of prevention strategies to most effectively address this problem [2,3] while noting the critical need for randomized clinical trial evidence in this area [4,5].

The potential association between various components of diet and cognitive function have been of interest [6]. In pre-clinical models, high-fat diets have hindered rodent memory performance and injured hippocampal neurons [7,8]. High-energy and high fat intake has been associated with cognitive deficits and dementia in some, but not all, observational studies [9−12]. However, a recent meta-analysis of prospective cohort studies found significant evidence of positive association between higher saturated fat intake and dementia risk [12]. The influence of a low-fat dietary pattern on global cognitive function has not previously been evaluated in a full scale, long term, randomized clinical trial setting.

The WHI DM trial provides an opportunity to evaluate whether a low-fat dietary pattern influences global cognitive function in a randomized, controlled clinical trial setting in a subset of 1606 study participants also enrolled in the Women's Health Initiative Memory Study (WHIMS) [13], where annual assessment of global cognitive assessment was performed through 8.5 years of the dietary intervention. Exploratory analyses examine subsequent risk of possible cognitive impairment followed by mortality (composite outcome) after cumulative 18.7 years (median) follow-up in WHIMS participants

2. Methods

Design details of the WHI DM trial have been described [14]. In the trial, 48,835 postmenopausal women between 50 and 79 years of age, were randomly assigned from 1993 to1998, to a dietary intervention group (40%; n = 19,541) designed to implement a low-fat dietary pattern with the primary goal of reducing dietary fat intake to 20% of energy while increasing intake of fruits, vegetables and grains or to a usual diet comparison group (60%; n = 29,294) [15]. Randomization was conducted at the WHI Clinical Coordinating Center. The protocol-specified co-primary endpoints were invasive breast cancer and colorectal cancer. Of these, 1606 study participants were also enrolled in WHIMS [13], an ancillary study to the two WHI clinical trials evaluating hormone therapy [14] where annual assessment of global cognitive function was performed during the 8.5 year (median) dietary intervention period. The WHI trials are registered at ClinicalTrials.gov:NCT00000611. Institutional Review Board (IRB) approval for each trial component was obtained at all the clinical centres and all participants provided written informed consent. The WHI Project Office at the US National Heart, Lung, and Blood Institute (NHLBI), the sponsor of this project, had no role in the preparation of this report.

For WHIMS participation, women had to be active in one of the WHI hormone therapy trials assessing estrogen plus progestin or estrogen alone, be 65 to 79 years of age, free of dementia, willing to undergo annual cognitive assessments, and willing to identify a friend or family member who could provide information about her functioning.

Between 1996 and 2007, WHIMS participants were tested at enrollment and annually thereafter by centrally trained, certified examiners, blinded to randomization status, for global cognitive functioning using the Modified Mini−Mental State Examination (3MSE) [16]. A detailed description of the WHIMS comprehensive multi-phase protocol for detecting probable dementia and mild cognitive impairment has been published [13]. Briefly, the test items measured temporal and spatial orientation, immediate and delayed recall, executive function, abstract reasoning, praxis, writing, and visuoconstructional abilities (copying). The 3MSE has demonstrated good sensitivity and specificity for detecting cognitive impairment [17,18]. After initial cognitive screening with the 3MSE, women that scored below an education-adjusted cut point [16,19] were identified as having possible cognitive impairment (considered as being cognitively vulnerable). Prior study has demonstrated ability of such screening tools to identify individuals with cognitive impairment [20].

Those with possible cognitive impairment received a comprehensive multi-phase evaluation which included administration of a comprehensive and validated neuropsychological battery [21], questionnaires regarding acquired cognitive and behavioral deficits and neuropsychiatric symptoms [22] and standardized neuropsychiatric evaluation by experienced local clinical experts (commonly neurologists, geriatricians or psychiatrists), who then reviewed this information and classified the women into one of three categories – no cognitive impairment, mild cognitive impairment or probable dementia [19,23]. For those classified as probable dementia, brain computed tomography and laboratory blood tests were used to rule out possible reversible causes. Final study classification of mild cognitive impairment or probable dementia was adjudicated at the WHIMS Clinical Coordinating Center at the Wake Forest University School of Medicine by a panel of dementia experts that included two neurologists, a geriatric psychiatrist and a geriatric psychologist. A supplemental case ascertainment protocol was developed and used to ascertain outcomes for deceased and/or proxy- dependent participants [24].

Dietary intervention group sessions were led by specially trained and certified nutritionists with 18 group sessions in year one and subsequent quarterly maintenance group sessions throughout the 8.5 year (median) dietary intervention period. Subsequently, all contact with study nutritionists ended as post-intervention follow-up began. During the intervention period, the percent reduction in energy from fat (8–10% decrease) and the increase in servings of fruits and vegetables and servings of grain were all statistically significant ($P < 0.001$) [15]. Although caloric restriction or weight loss were not intervention targets, an early statistically significant weight loss (3%) emerged in the intervention group.

The primary study analysis was dietary modification influence on global cognitive function (failed cognitive function screening as possible cognitive impairment) in WHIMS participants through the protocol defined 8.5 year dietary intervention period. Also, in an exploratory analysis, we examined deaths from all-causes after possible cognitive impairment in WHIMS participants through 18.7 years (median) cumulative follow-up.

Cumulative follow-up (intervention plus post-intervention phases) included deaths through December 31, 2016 (median [Q1-Q3], 18.7 [14.6–19.5] years cumulatively) with mortality ascertained by regular surveillance of the cohort with deaths documented by through the National Death Index (NDI) and by Information reports of next of kin or the postal service. NDI searches were conducted at nine time points before 2018 for all participants with unknown vital status.

2.1. Statistical analysis

The current study analyses were not protocol pre-specified. The primary endpoint of possible cognitive impairment and the exploratory composite endpoint of death from all causes after possible cognitive impairment in WHIMS participants were assessed by randomly assigned DM intervention group by dividing the number of events by the corresponding person-time elapsed from randomization in each period. HRs contrasting the intervention and comparison groups by diagnosis of possible cognitive impairment (no cognitive impairment/mild cognitive impairment/probable dementia) were estimated using competing risk models that included cause-specific baseline hazard functions and hazard ratios [25]. Cumulative hazard curves were generated, and HRs and 95% CIs and P values computed using Cox regression models stratified on age group in 5-year categories, race/ethnicity, education, and randomization status in the WHI hormone therapy trials. The endpoint of possible cognitive impairment was assessed through 8.5 years follow-up during the dietary intervention period when annual assessment of global cognitive function was available. WHIMS participants contributed follow-up time until the end of DM intervention phase, date of possible cognitive impairment, loss to follow-up, or death, whichever came first. The composite endpoint of death after possible cognitive impairment was assessed from randomization through the available 18.7 year (median) follow-up period, where participants without possible cognitive impairment were censored at the end of the intervention phase or death (whichever came first), since they were no longer at risk for the composite endpoint, while those with an impairment contributed follow-up time until death or December 31, 2016 (Fig. 1), the last date covered by the NDI linkage. This type of composite endpoint has been used elsewhere in the context of breast cancer progression [26–28], described thoroughly [29], utilize usual indicator variables for event status (1 = time to composite event was observed; 0 = observation was censored), and can be fit with the usual Cox regression software implementations.

All statistical tests are 2-sided and nominal *P* values of 0.05 or less are regarded as statistically significant. P-values do not adjust for multiple outcomes. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc.) and R software version 3.4 (R Foundation for Statistical Computing). As dietary intervention effects were examined in 11 subgroup analyses, less than one statistically significant interaction was expected by chance alone ($\leq 11 \times 0.05$) [30].

3. Results

Baseline characteristics of WHIMS participants, including demographic, medical history, and dietary variables were well balanced between randomization groups (Table 1). Briefly, women were, on average, 69.9 years of age, somewhat overweight with median BMI of 29.5 kg/m^2 and 29% had a college degree or higher. Characteristics associated with risk of cognitive impairment and dementia including age, education, smoking status, stroke history, diabetes, hormone use, waist circumference, blood pressure, body mass index, and aspirin use were also well-balanced between the two groups. Participant flow through cumulative follow-up is outlined in Fig. 1. After one year of dietary intervention, changes in the 1606 participants with cognitive function assessment reflected findings in the overall group, namely statistically significant reduction in percent calories fat, and increasing from and vegetable intake and, although not protocol target decreased weight and waist circumference (Table 2).

At entry, the distribution of baseline 3MSE scores (0 worst to 100 best) was notably left (negative)-skewed with median (Q1-Q3) = 96.0 (94.0, 98.0), but well balanced between groups. During median (Q1-Q3) follow-up of 7.2 (6.0–8 0) years following WHIMS enrollment, while annual global cognitive function assessment was ongoing during the dietary intervention period, there were 126 incident cases of possible cognitive impairment identified with 41 (0.94%) in the intervention group and 85 (1.37%) in the comparison group; the dietary intervention resulted in a statistically significant reduction in the incidence of possible cognitive impairment with a HR 0.59 (95%CI 0.38–0.91, $P = 0.01$) (Fig. 2).

Kaplan-Meier estimates of the cumulative hazard curves for possible cognitive impairment during the intervention period are depicted in Fig. 3. As seen, in the comparison group, there is a year-to-year increase in the risk of exceeding the target threshold for cognitive performance in 3MSE resulting in a designation of possible cognitive impairment of about 1.5% per year, with early separation (by year 2) with lower risk seen in the intervention group. Of the 126 participants identified with possible cognitive function impairment, after further comprehensive neurological assessment, 59% were categorized as having mild cognitive impairment or probable dementia; for findings in the dietary intervention versus comparison groups, HR was 0.65 (95% CI 0.35–1.19) for mild cognitive impairment and HR of 0.63 (95% CI 0.19–2.10) for probable dementia (bottom panel of Fig. 2) while the remaining women were categorized as having no cognitive impairment. Combining confirmation of mild cognitive impairment or probable dementia (27 v 47 events) yields an HR of 0.65 (95%CI 0.38–1.11).

The dietary influence on possible cognitive impairment was most evident among women in the lowest quartile of 3MSE score at WHIMS enrollment, identifying those with lower global cognitive function (HR 0.43 95% CI 0.22–0.84) as the influence diminished with

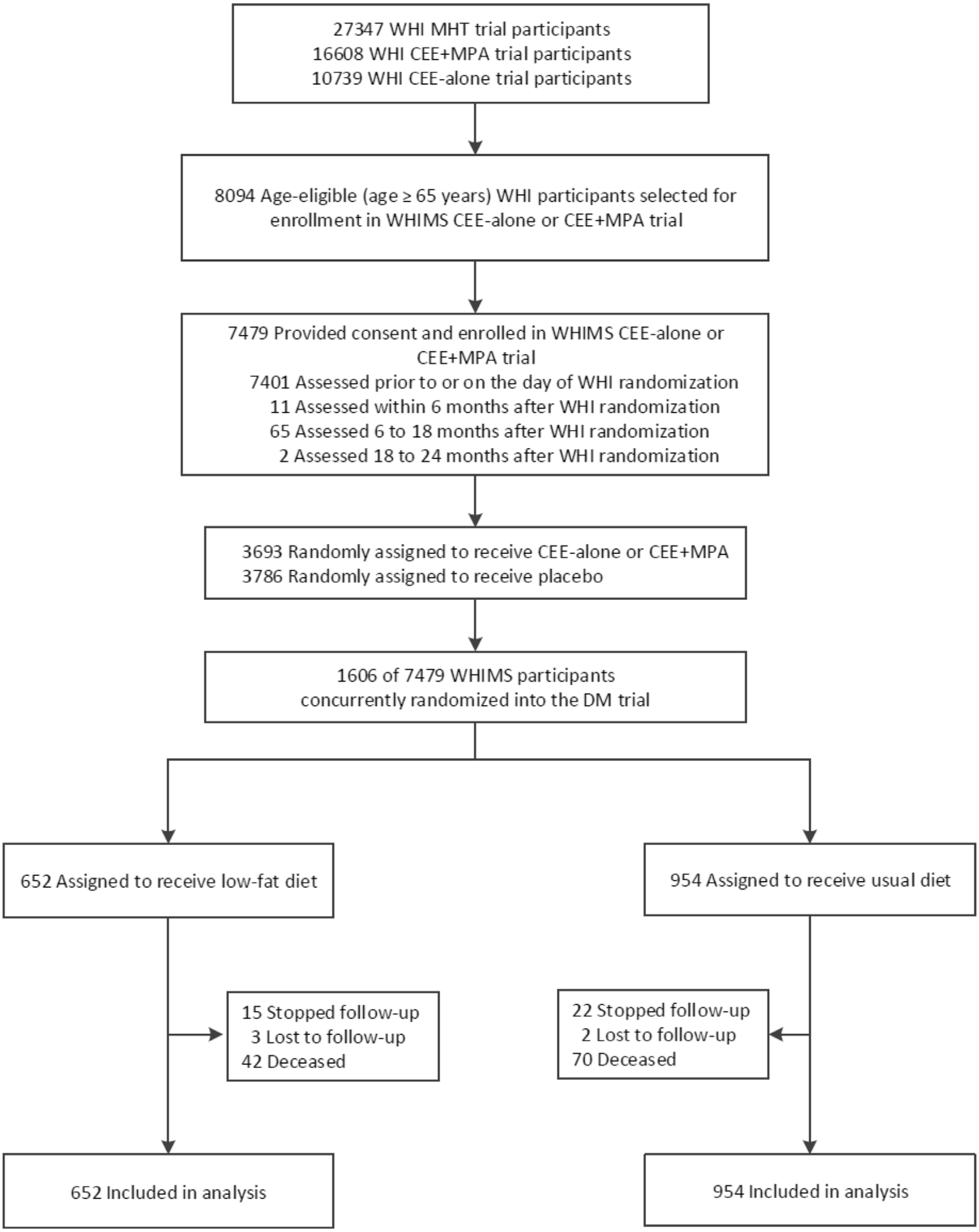

Fig. 1. Participant flow diagram for the low-fat dietary intervention phase among the subset of DM trial participants that participated in WHIMS (n = 1606), an age eligible subset (age ≥ 65 years) of the WHI MHT trials. WHIMS = Women's Health Initiative Memory Study; MHT = menopausal hormone therapy; CEE = conjugated equine estrogen; MPA = medroxyprogesterone acetate.

increasing 3MSE score (P interaction = 0.05) (Fig. 2). This result was explored further by assessing the dietary influence on year-to-year mean change in 3MSE score as a measure of global cognitive function stratified by baseline 3MSE quartiles. Although the overall influence of the dietary intervention on 3MSE change score was not significant, mean (95% CI) = 0.1 (−0.2 to 0.4) with P = 0.47, there was a significant interaction between randomization group and baseline 3MSE score (quartile; P = 0.02, based on test of linear-trend of group means (Supplemental Figure). Specifically, dietary intervention resulted in an increase in 3MSE score beginning in year two among women with low baseline 3MSE score corroborating the favorable effect of dietary intervention seen on possible cognitive impairment in the same low 3MSE score subgroup; mean change score during follow-up was mean (95% CI) = 0.7(0.1 to 1.3). In contrast, the mean change scores for increasing quartiles did not suggest a difference; mean (95% CI) = 0.2(−0.5, 0.9), −0.3(−0.9, 0.3) and −0.04(−0.5, 0.4), respectively. Suggestions of a heterogeneous influence for diet was not observed in any of the

Table 1
Baseline characteristics of DM trial participants that participated in WHIMS (n = 1606).

	No. and% of Participants[1]			
	Intervention (N = 652)		Comparison (N = 954)	
Characteristic				
Age at screening (y), mean, SD	69.9	3.7	69.9	3.6
Age group at screening, *y*				
60–69	343	52.6	501	52.5
70–79	309	47.4	453	47.5
Race/ethnicity				
White	557	85.4	819	85.8
Black	53	8.1	90	9.4
Hispanic	25	3.8	20	2.1
American Indian	0	0.0	3	0.3
Asian/Pacific Islander	6	0.9	10	1.0
Unknown	11	1.7	12	1.3
Education				
< High school	51	7.8	67	7.0
High school diploma/GED	134	20.6	221	23.2
School after high school	266	40.8	400	41.9
College degree or higher	201	30.8	266	27.9
Smoking				
Never	346	53.9	540	57.1
Past	254	39.6	354	37.5
Current	42	6.5	51	5.4
Stroke	9	1.4	18	1.9
Diabetes	61	9.4	93	9.7
Hormone use				
Never	437	67.0	662	69.4
Past	169	25.9	233	24.4
Current	46	7.1	59	6.2
Waist circumference (cm), mean, SD	92.0	13.2	92.7	13.0
Systolic BP (mm Hg), mean, SD	132.8	17.3	133.3	17.9
Diastolic BP (mm Hg), mean, SD	75.3	9.0	76.0	8.9
Body mass index[2], median (Q1-Q3), IQR	29.3	25.7–33.4	29.8	26.3–33.8
3MSE score, median (Q1-Q3), IQR	96.0	94.0–98.0	96.0	93.0–98.0
Hypertensive (Self-report or high BP)	329	50.6	538	56.7
Aspirin use (≥ 80 mg for ≥30 days)	136	20.9	233	24.4
MHT randomization group				
CEE-alone	119	18.3	218	22.9
CEE-alone placebo	126	19.3	218	22.9
CEE+MPA	188	28.8	265	27.8
CEE+MPA placebo	219	33.6	253	26.5
Percent energy from total fat (%), mean, SD	37.8	5.0	38.3	5.3
Percent energy from protein (%), mean, SD	16.4	3.0	16.5	3.0
Percent energy from carbohydrates (%), mean, SD	45.9	6.3	45.1	6.4
Fruit and vegetable intake (med serv/day), mean, SD	3.8	2.0	3.7	1.9

[1] Values are reported as No. and% unless otherwise indicated.
[2] Calculated as weight in kilograms divided by height in meters squared.

remaining subgroups explored (Fig. 2); none of the corresponding interactions were statistically significant.

The clinical significance of screening positive for possible cognitive impairment was examined for subsequent mortality risk (death from all causes) through 18.7 years median follow-up by cognitive function category: normal (never failed 3MSE screening, n = 1480), no cognitive impairment (but failed screening as possible cognitive impairment, n = 52); mild cognitive impairment (n = 57); and probable dementia (n = 17). Subsequent mortality by group was 46%, 58%, 61%, and 100%, respectively. Thus, the designation of possible cognitive impairment likely identifies a population of clinical relevance.

Table 2
Change characteristics of DM trial participants that participated in WHIMS (n = 1606).

	Intervention (N = 652)		Comparison (N = 954)		
Post-randomization variables	Mean	SD	Mean	SD	P-Value
Change in percent energy from:					
Total fat (%)	−12.3	7.8	−1.6	6.2	<0.001
Saturated fat (%)	−4.3	3.3	−0.6	2.6	<0.001
Polyunsaturated fat (%)	−2.3	2.1	−0.2	2.1	<0.001
Monounsaturated fat (%)	−4.9	3.3	−0.6	2.8	<0.001
Trans-fat (%)	−1.0	1.2	−0.1	1.2	<0.001
Carbohydrates (%)	11.7	9.0	1.6	6.9	<0.001
Protein (%)	1.3	3.2	0.1	2.9	<0.001
Animal protein (%)	0.3	3.6	0.0	3.1	0.12
Vegetable protein (%)	1.0	1.2	0.1	1.0	<0.001
Alcohol (%)	0.1	2.4	0.1	2.1	0.83
Change in other dietary characteristics:					
Vegetable and fruit (med serv/day)	1.3	2.3	0.2	1.8	<0.001
Grains (med serv/day)	0.0	2.6	−0.6	2.3	<0.001
Dietary fiber (g)	2.2	6.9	−0.5	5.7	<0.001
Cholesterol (mg)	−92.1	147.7	−26.5	132.4	<0.001
Change in participant characteristics:					
Weight (kg)	−2.1	11.9	0.1	10.0	<0.001
Waist (cm)	−1.7	5.8	−0.4	6.1	<0.001
Systolic BP (mm Hg)	−3.6	15.0	−2.1	17.7	0.10
Diastolic BP (mm Hg)	−2.8	8.7	−2.0	9.2	0.07

Exploratory analyses found deaths from all-causes after possible cognitive impairment was non-significantly lower for the intervention versus comparison group (0.56% vs 0.77%, HR 0.83 95% CI 0.35 to 2.00, P = 0.16).

4. Discussion

In the WHI Dietary Modification randomized clinical trial evaluating a low-fat dietary pattern, in a subgroup of 1606 postmenopausal women also enrolled in the WHI Memory Study (WHIMS) having annual assessment of global cognitive function, adoption of a low-fat dietary pattern significantly reduced the risk of possible cognitive impairment based on the findings from serial 3MSE results. Subsequent neurological assessment of those with possible cognitive impairment diagnosed 59% with either mild cognitive impairment (45%) or probable dementia (14%). As exploratory analyses were suggestive of a higher mortality risk in women with possible cognitive impairment, even in the absence of mild cognitive impairment or probable dementia, compared to women without such findings, those failing 3MSE screening likely identifies a population of clinical relevance.

The significant reduction in possible cognitive impairment (HR 0.59 95% CI 0.38–0.91, P = 0.01) in the dietary intervention group was followed by a smaller non-significant reduction in deaths after possible impairment (HR = 0.83), suggest that a post-impairment survival benefit is unlikely [29]. These results are consistent with the hypothesis offered by Feart and colleagues [31] in response to their cohort study finding that higher Mediterranean diet adherence was associated with slower cognitive decline but not with dementia. They suggested that the Mediterranean diet may have a beneficial effect during the prodromal phase of dementia, rather than the last few years preceding diagnosis, after which pathophysiological processes cannot be reversed by diet. Such findings suggest lifestyle interventions may have most effect when begun by individuals without cognitive impairment.

The favorable dietary effect of reducing the incidence of possible cognitive impairment was greater in women with lower, less favorable, baseline 3MSE scores, a finding supported by serial year-to-year analyses of global cognitive function where a statistically significant interaction suggests more favorable diet effect in the group with

	Intervention N(%)	Comparison N(%)	HR(95%CI)	P
Overall effect on possible cognitive impairment*	**41(0.94)**	**85(1.37)**	**0.59(0.38,0.91)**	**0.01**
Participant characteristics				
Age at randomization				**0.15**
65−69	12(0.51)	34(1.01)	0.39(0.19,0.81)	
70−79	29(1.45)	51(1.79)	0.76(0.44,1.30)	
Race/ethnicity				**0.35**
White	22(0.58)	49(0.89)	0.70(0.42,1.17)	
Black	13(4.24)	25(5.23)	0.52(0.21,1.28)	
Other	6(2.25)	11(4.32)	0.22(0.04,1.08)	
Education				**0.57**
< High school	14(5.03)	18(4.91)	0.99(0.41,2.38)	
High school/GED	7(0.75)	23(1.64)	0.42(0.17,1.07)	
School after high school	12(0.69)	26(0.96)	0.58(0.26,1.28)	
College degree or higher	8(0.57)	18(1.04)	0.49(0.20,1.23)	
Smoking				**0.61**
Never	18(0.76)	53(1.51)	0.46(0.24,0.87)	
Past	16(0.97)	24(1.02)	0.79(0.33,1.91)	
Current	5(1.87)	6(1.88)	0.71(0.04,11.79)	
Menopausal hormone use†				**0.53**
No	13(0.91)	29(1.33)	0.45(0.19,1.04)	
Yes	28(0.96)	56(1.39)	0.62(0.35,1.11)	
Randomized to CEE or CEE+MPA^				**0.62**
No	22(0.97)	39(1.27)	0.53(0.29,0.97)	
Yes	19(0.92)	46(1.47)	0.66(0.36,1.22)	
BMI(kg/m2)				**0.07**
<25	7(0.75)	23(2.20)	0.28(0.08,1.01)	
25−<30	12(0.83)	31(1.45)	0.53(0.23,1.21)	
30−<35	13(1.11)	20(1.08)	1.63(0.65,4.08)	
>=35	9(1.16)	10(0.86)	0.69(0.15,3.13)	
Waist >=88cm				**0.12**
No	11(0.61)	38(1.71)	0.37(0.15,0.94)	
Yes	30(1.19)	47(1.18)	0.88(0.51,1.52)	
Hypertension				**0.08**
No	15(0.68)	40(1.46)	0.35(0.16,0.75)	
Yes	26(1.23)	44(1.28)	0.84(0.45,1.57)	
Diabetes ever				**0.40**
No	34(0.85)	70(1.23)	0.55(0.33,0.91)	
Yes	7(1.90)	15(2.85)	0.94(0.30,2.97)	
Baseline 3MSE score (quartiles)				**0.05**
<94	23(2.66)	60(4.36)	0.43(0.22,0.84)	
94−<96	6(0.77)	9(1.06)	0.50(0.12,2.10)	
96−<98	6(0.58)	8(0.54)	1.01(0.27,3.73)	
>=98	5(0.31)	6(0.25)	1.83(0.44,7.59)	
Diagnosis of possible cognitive impairment				**0.86**
No cognitive impairment	**14(0.32)**	**38(0.61)**	**0.50(0.25,1.03)**	
Mild cognitive impairment	**20(0.46)**	**37(0.60)**	**0.65(0.35,1.19)**	
Probable dementia	**7(0.16)**	**10(0.16)**	**0.63(0.19,2.10)**	

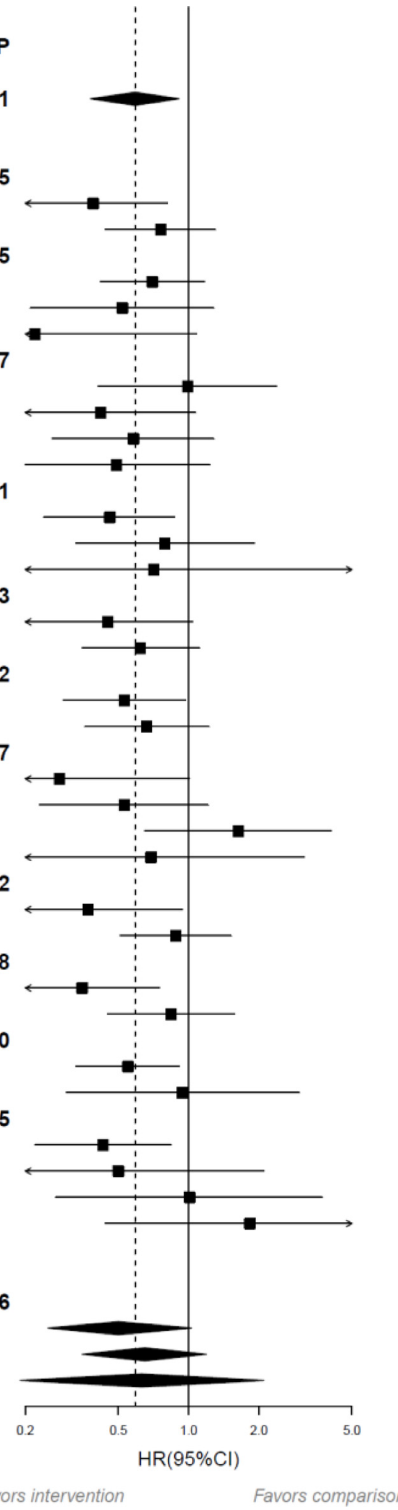

Fig. 2. Overall influence of the low-fat dietary intervention on possible cognitive impairment* during the intervention phase among the subset of DM trial participants that participated in WHIMS (*n* = 1606). The 7-year follow-up is over the dietary intervention phase of the trial (median, 7.2 [interquartile range {IQR}, 6.0−8.0] years). Summary statistics computed from Cox regression models stratified by 5-year age group, race/ethnicity, education, and randomization status in the WHI hormone therapy trials, using time from randomization as the time-scale. Subgroups were investigated, one at a time, by including an interaction term between randomization arm and subgroup with additional stratification of the baseline hazard by corresponding subgroup. P values corresponds to a two-sided score (log-rank) test of the dietary intervention's overall influence, or for the subgroup analysis, a test of interaction between the randomization group and corresponding subgroup. Percentages are annualized. * Possible cognitive impairment defined as transition to Phase 2 of the WHIMS protocol. After completion of Phases 2 and 3, typically within 3 months possible cognitive impairment, participants were classified as probable dementia, mild cognitive impairment, or no cognitive impairment. † Ever used menopausal hormone therapy or randomized to CEE or CEE+MPA arm of WHI hormone trial. ^ Among women randomized to either WHI hormone therapy trial. WHIMS = Women's Health Initiative Memory Study; HR = hazard ratio; CI = confidence interval.

lowest baseline 3MSE scores. Comparatively less favorable results among women having higher baseline 3MSE scores may represent a limitation of the 3MSE assessment. For example, the top quartile of women have scores ≥ 98 leaving little/no room for improvement against an upper 3MSE score limit of 100. Subgroup analyses should be interpreted with caution because of multiple comparisons.

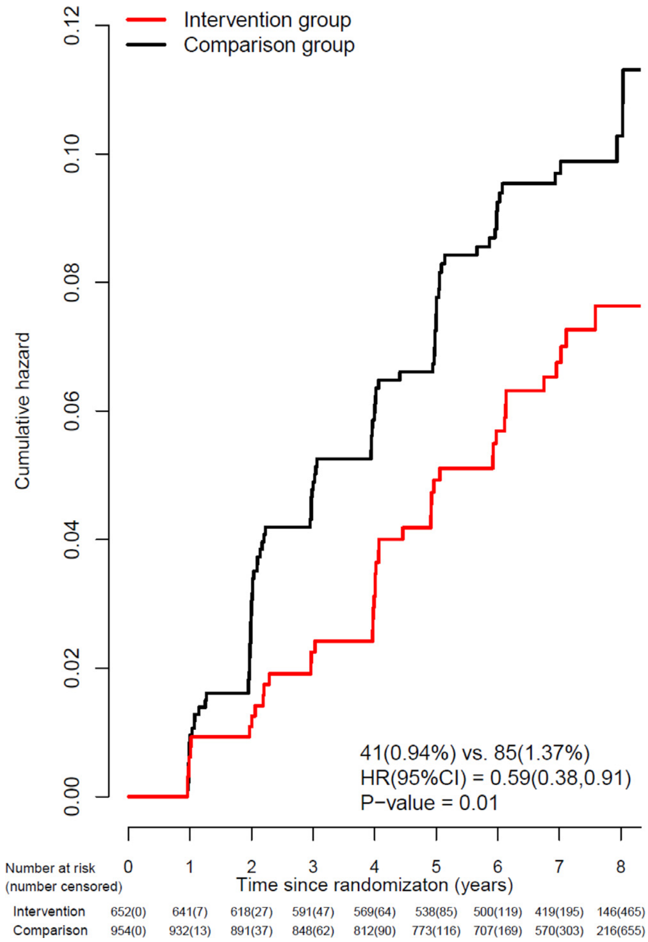

Fig. 3. Kaplan-Meier estimates of the cumulative hazard for possible cognitive impairment* during the intervention phase among the subset of DM trial participants that participated in WHIMS (*n* = 1606). The 7-year follow-up is over the dietary intervention phase of the trial (median, 7.2 [interquartile range {IQR}, 6.0–8.0] years). Summary statistics computed from a Cox regression model stratified by 5-year age group, race/ethnicity, education, and randomization status in the WHI hormone therapy trials, using time from randomization as the time-scale. *P*-value corresponds to a two-sided score (log-rank) test of the dietary intervention's overall influence. Percentages are annualized. * Possible cognitive impairment defined as transition to Phase 2 of the WHIMS protocol. After completion of Phases 2 and 3, typically within 3 months of possible cognitive impairment, participants were classified as probable dementia, mild cognitive impairment, or no cognitive impairment. WHIMS = Women's Health Initiative Memory Study; HR = hazard ratio; CI = confidence interval.

Review of observational study findings has associated higher adherence to the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean -DASH Intervention for Neurodegenerative Delay (MIND) diets with less cognitive decline [32,33]. However, few randomized trials have evaluated nutrition based interventions in relation to cognition and most have been limited in size and duration [6].

The 2010 National Institutes of Health Evidence Report on Preventing Alzheimer's Disease and Cognitive Decline [34] proposed criteria for future randomized clinical trials which included intervention duration of at least one year and size of ≥500 participants. Using these criteria, we identified four prior randomized trials assessing a dietary intervention with or without other intervention components with design and findings outlined in Table 3. Three [35–37] of four trials entered participants with cognitive dysfunction or those at high risk for cognitive dysfunction or vascular disease. Intervention durations were 1 year [38], 2 years [36], 3 years [37] and 6.5 years [35]. Each of the four trials used different cognitive function endpoints. All presented baseline and final endpoint assessments precluding determination of trajectory of cognitive dysfunction over time. None of the trials evaluated a low-fat eating pattern.

Two of the four trials had positive findings. The FINish GERiatric Intervention Study (FINGER) was a mutidomain intervention (diet, exercise, cognitive training, and vascular risk monitoring) involving 1260 participants. The dietary component included recommendations for 10–20% of energy from protein, 25–35% of energy from fat with targets for specific fat types and energy intake reduction facilitating 5–10% body weight reduction if needed. The intervention resulted in improved or maintained cognition over the two year study duration [36]. The second study with positive findings presents a subsample report from one of 12 recruitment centres of the PREvencion con Dieta MEDiterranea (PREDIMED) where effects of a Mediterranean diet influence on cognitive function diet was assessed against a "low fat" control diet with 522 participants randomized across three interventions. As no decrease in dietary fat intake was reported in the "low fat" group, PREDIMED operationally had a usual diet control. In any event, a Mediterranean diet enhanced with either extra-virgin olive oil or nuts appeared to improve cognition compared to the control condition [35]. Of these larger randomized trials, three of four entered participants at cognitive function risk while three of four reported findings after interventions of three years or less.

The current report adds to the emerging evidence that dietary intake can influence cognitive function in a randomized trial involving relatively healthy postmenopausal women not selected for cognitive risk and followed over a long period. In this setting, findings from the WHI DM trial indicate that dietary fat intake reduction may also be a factor to be incorporated in future dietary recommendations.

The WHI DM low-fat dietary plan is somewhat similar to the Dietary Approach to Stopping Hypertension (DASH) which includes recommendations to increase fruits, vegetables and grains, use no/low fat dairy products, and reduce total fat intake [39]. While the WHI DM low-fat dietary plan does provide more emphasis on total fat reduction than DASH, it can still be best described as one of dietary moderation not requiring extreme change.

The WHI DM finding of a favorable effect of a low- fat dietary pattern on possible cognitive impairment is also similar in many respects to, and supportive of, the most recent World Health Organization (WHO) Guidelines for Risk reduction of Cognitive Decline and Dementia [40]. Their recommendation for a healthy diet includes five portions of fruits, vegetables and whole grains a day and less than 30% of total energy intake from fats. Additionally, the guideline specifically recommends the Mediterranean diet as "more effective than usual care in reducing risk/progression of cognitive decline and/or dementia" [40].

The dietary changes of the WHIMS subset in the dietary intervention reflect those achieved by women in the entire dietary intervention group. After one year, the percent energy from fat was 24.3% (mean [SD] 7.5%) [15] and remained statistically significantly different than the control group throughout the 8.5 year intervention where, at final assessment, level was 29.8% [8.3] [41]. These levels are not much different from the average US intake of postmenopausal women of 33%. While statistically significant, the increase in fruit and vegetable intake was modest with an increase from about four to five servings per day for each and achieved WHO nutritional recommendations. Although not an intervention target, a statistically significant weight loss difference of between 1.9 to 0.4 kg, compared to the control group, was maintained throughout the dietary intervention period. The modest dietary changes of the WHI Dietary Modification trial should be easily achievable by most postmenopausal women.

Study strengths include the randomized design, a population of postmenopausal women, not selected for cognitive dysfunction, dietary program adherence supported by body weight and biomarker differences [15] carefully designed and implemented procedures

Table 3
Randomized trials of dietary/multidomain interventions and cognition.

Name		Eligibility	N	Intervention	Duration	Endpoint	Outcome
FINGER Lance 2015t	**FIN**nish **GER**iatric Intervention Study to Prevent Cognitive Impairment and Disability	60–70 years old Cardiovascular Risk Factors Aging and Dementia score (CAIDE) ≥ 6 points	1260 46% Female	Diet, exercise, cognitive training, vascular risk monitoring versus control	2 years	Neuropsychological test battery (NTB) Z score	NTB score higher in Intervention $P = 0.030$
MAPT Lancet Neurology 2017	**M**ultidomain **A**lzheimer **P**revention **T**rial	70+ years old 1) Memory complaints 2) Limitations in ADL or 3) Slow gait	1525 65% Female	4 arms, Multidomain (MD) +placebo; Omega 3 FA alone; MD + Omega 3 FA; placebo	3 years	Composite Z score Combining 4 cognitive tests	No significant effect on cognitive decline compared to placebo
NU-AGE Diet Frontier in Physiology 2018	New dietary strategies addressing the specific needs of the elderly population for healthy ageing in Europe	67–79 years old Free of dementia relatively healthy older adults	1279 100% Female	NU-AGE DIET, Medi, like versus usual diet control	1 year	Cognitive function Mini-Mental State Examination (MMSE) Plus CERAD score	No overall difference Higher adheres Improvement in global function
PREDIMED-NAVARRA J Neurol Neurosurg Psychiatry 2013	Prevención con Dieta Mediterránea	Age 75 years (mean) High vascular risk	522 55% Female	3 arms, 2 MedDiets ± extra-virgin olive oil or mixed nuts versus "low fat" control**	6.5 years	Mini-Mental State Examination (MMSE) plus Clock Drawing Test (CDT)	MedDiets higher than control MMSE, $P = 0.005$ CDT, $P = 0.001$

assessing possible cognitive impairment, annual assessment of Global cognitive function providing information on trajectory of cognitive change, and a long follow-up period to support exploratory analyses regarding implications for mortality.

Limitations include those associated with secondary analyses. These analyses are exploratory and should be viewed as hypothesis-generating, requiring reassessment in prospectively conducted confirmatory trials. While mild cognitive impairment or probable dementia would have been a more meaningful endpoint, we were limited by available sample size. The parent cohort, WHIMS ($n = 7479$), was designed to have 80% power to detect an influence on all-cause dementia. In addition, this study relied on the 3MSE, while other instruments such as the Montreal Cognitive Assessment (MoCA) [42] may better detect mild cognitive impairment. The WHI low-fat dietary program reduced fat and commensurately increased fruit, vegetable and grain consumption, therefore the effects of these increases cannot be separated from the effects of reduced fat. Also, social participation and support are strongly connected to good health and well-being, so the sustained cognitive engagement by nutritionist led intervention sessions could have had some positive influence independent of dietary change. However, there is insufficient evidence regarding social activity and risk-reduction for risk of cognitive decline. As linkage with Medicare provides more comprehensive assessment of dementia outcomes [43], a future analysis will examine the low-fat dietary pattern influence on dementia incidence and dementia mortality, in all 48,835 study participants.

As diabetes [44] and the metabolic syndrome have been associated with higher dementia risk [45], the favorable WHI dietary intervention effects on the course of diabetes [41], hypertension [46], other metabolic syndrome components [47] and weight management [48], represent potential mediators of the cognitive effects seen.

In summary, adoption of a low-fat dietary pattern, representing dietary moderation, significantly reduced risk of possible cognitive impairment in postmenopausal women. Subsequent mortality findings suggest the designation of possible cognitive impairment likely identifies a higher risk population of clinical relevance.

Women's Health Initiative (WHI) Data Sharing Statement:

Item[1]	WHI statement
Will individual participant data be available (including data dictionaries)?	Deidentified individual participant data is available.
What data in particular will be shared?	All of the deidentified participant data collected during the trial.
What other documents will be available?	Study protocol, study procedures, data collection forms and other documents.
When will data be available (start and end dates)?	Data is available through the WHI online resource, https://www.whi.org/researchers/data/Pages/Home.aspx, while the WHI remains funded[2] and indefinitely through BioLINCC, https://biolincc.nhlbi.nih.gov/studies/whict/.
With whom?	Eligible researchers[3] may download the data directly at the WHI online resource. Other researchers may download the publicly available data through BioLINCC, in accordance with NHLBI's BioLINCC guidelines.
For what types of analyses?	Eligible researchers[3] with an approved specified purpose. Other researchers in accordance with NHLBI's BioLINCC guidelines.
By what mechanism will data be made available?	Data are available at the aforementioned links.

[1]Items correspond to those specified in: Taichman, D.B., Sahni, P., Pinborg, A., Peiperl, L., Laine, C., James, A., Hong, S.T., Haileamlak, A., Gollogly, L., Godlee, F. and Frizelle, F.A., 2017. Data sharing statements for clinical trials: a requirement of the International Committee of Medical Journal Editors. Annals of internal medicine, 167(1), pp. 63–65.

[2]Currently through 2020.

[3]See https://www.whi.org/researchers/data/Pages/Home.aspx for eligibility.

Declaration of competing interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Chlebowski reported being a consultant for Novartis, AstraZeneca, Immunomedics, Amgen, Puma and Genentech.

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Program office

(National Heart, Lung, and Blood Institute, Bethesda, MD) Jacques Rossouw, Shari Ludlum, Dale Burden, Joan McGowan, Leslie Ford, and Nancy Geller.

Additional information

A full list of all the investigators who have contributed to Women's Health Initiative science appears at: https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pd.

Trial registration

Clinicaltrials.gov Identifier: NCT00000611.

The research protocol

Available at: https://www.whi.org/about/SitePages/Dietary%20Trial.aspx.

Role of the funding source

Representatives from National Heart, Lung and Blood Institute (NHLBI) had a role in the design and conduct of the study but played no role in data interpretation, writing of the report or the decision to submit for publication. RTC had full access to all study data and had final responsibility for the decision to submit for publication.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2019.100240.

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